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**A European multicentre survey of impulse control behaviours in Parkinson's disease patients treated with short- and long-acting dopamine agonists**

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## Abstract

**Background:** Impulse control disorders (ICDs) in Parkinson's disease (PD) are associated primarily with dopamine agonist (DA) use. Comparative surveys of clinical occurrence of impulse control behaviours on longer acting/transdermal DA therapy across age ranges are lacking.

**Objective:** The aim of this study was to assess the occurrence of ICDs in PD patients across several European centres treated with short- or long-acting and transdermal DAs (Rotigotine skin patch (RTG); Ropinirole extended release (ROP-XL); Pramipexole prolonged release (PPX- PR)) based on clinical survey as part of routine clinical care.

**Methods:** A medical record- and clinical interview-based survey of patients initiating or initiated on DA treatment (both short- and long-acting, and transdermal) across a broad range of disease stages and age groups.

**Results:** 425 cases were included (mean age= 68.3 years (range 37-90), mean duration of disease=7.5 years (range 0-37)). ICD frequencies (as assessed by clinical interview) were significantly lower with RTG (4.9%;  $p<0.05$ ) compared with all other assessed DAs, except for PPX-PR. Rate of ICDs for PPX-PR (6.6%) were significantly lower than PPX-IR (19.0%;  $p<0.05$ ). Discontinuation rates of DA therapy due to ICDs were low.

**Conclusions:** Our data suggest a relatively lower rate of ICDs with long-acting or transdermal DAs, but these preliminary observational data need to be confirmed with prospective studies controlling for possible confounding factors.

**Introduction**

Dopamine agonists (DAs) are an important therapeutic option in the management of Parkinson's disease (PD). Long-acting formulations have been developed, on the presumption that this decreases motor complications as well as improves adherence to therapy [1-3].

Three prolonged release (PR) DAs, two oral (Ropinirole (ROP) and Pramipexole (PPX)) and one transdermal (TD; Rotigotine (RTG) patch), are in theory capable of delivering continuous drug delivery, although with PR ROP and PPX the plasma levels dip after 14-17 hours [4], while RTG appears to provide coverage over 24 hours as long the patch is continuously applied. Some aspects of long acting DAs use are poorly researched including the fact that it is not known whether impulse control disorders (ICDs) occur at the same rate in those exclusively or predominantly using PR DAs compared with immediate release (IR) DAs.

In general, ICDs have been reported with the use of IR DAs in PD showing a cross-sectional prevalence rate of 17% (DOMINION study) [5], but PR DAs have only recently become available and such data are not published.

A recent retrospective study on the topic reported that oral DAs (ROP and PPX) treatment might be associated with an increased risk of developing ICDs compared with TD DA (RTG) treatment [6].

Here we report results from a multicentre observational study in a PD population in routine clinical care, called the European Dopamine Agonist (IR and PR) Impulse Control Evaluation (DAICE) study. To our knowledge this is the first multicentre observational comparative study reporting on the occurrence of ICDs, including both IR and PR formulations (oral and TD).

**Patients and Methods**

**Design**

This was a retrospective and prospective medical record- and clinical interview-based survey (and not an intention to treat study) of PD patients in routine clinical care across different disease stages and ages who initiated DA treatment, with a focus on PR (oral and TD) formulations. As this was an observational survey, all data collected were based on outcomes generated from routine clinical practice in clinics between 2010 and 2012, with medications being started at the discretion of the treating clinician based on the patient's clinical status.

**Patients**

Data from 425 PD patients diagnosed according to the UK brain bank criteria [7] were included. Data were collected from patients already taking ROP-IR/XL, PPX-IR/PR and RTG, as well as those initiating treatment with these DAs. Patients were assessed from 8

European centres (in the UK, Spain, Denmark and Romania) being part of EUROPAR, a European collaboration of the PD non-motor symptoms (NMS) research now adopted as part of the International Parkinson and Movement Disorder Society (IPMDS) Non Motor Study Group. This was a convenience sample of patients willing to take part in the data survey. Patients who had dementia or Parkinsonism not due to idiopathic PD were excluded.

### Setting and locations

This study was conducted in departments of Neurology and Movement Disorder Units from collaborating centres in Europe being part of EUROPAR and the newly formed IPMDS Non Motor Study Group collaboration.

### Ethical aspects

This medical record survey was registered as an audit (medical record review) (Code number: AP1198-01), and the prospective component was part of a longitudinal study of motor and non-motor symptoms in PD and the impact of PD treatments (NILS: UKCRN No 10084). Ethical approval for NILS was obtained at all local research institutions.

### Assessments

Assessment was based on established clinical records and chart review. For each patient socio-demographic and clinical data were collected from the charts, including: sex, age, documented PD diagnosis, and duration of disease, age at PD onset, past use of DAs (dose and duration), discontinuation of past DAs and reason for discontinuation, duration of current DA use, use of any other antiparkinsonian medication, and co-morbid conditions.

We used the data collected from completion of the NMS Questionnaire while waiting to be seen for a clinical appointment [8] in our patients as is recommended by some learned societies and patient charities. In all participating centres, during clinical consultation, ICDs were specifically asked about and documented. The diagnosis of ICD or alternative side effects was not done by a formal application of an instrument, but based on the assessment and judgment of the individual clinicians; all experienced non motor researchers. If based on clinical assessment and interview, the clinician felt that ICD were present, the clinician then enquired about specific types such as compulsive gambling, hypersexuality, binge eating (including nighttime eating and chocolate-philia), hobbyisms (compulsive shopping, internet use or any other as reported) and whether multiple ICDs co-existed. Specifically, clinically relevant ICDs were also noted using the item 18 of NMS Questionnaire (feeling less interested in sex or more interested in sex) to address hypersexuality and further interview by an experienced clinician to address other relevant ICDs as reported in the results.

Information regarding timing of the onset of ICDs as well as any additional side effects which led to discontinuation of DA therapies (as documented in charts) were recorded. Furthermore, all clinicians also noted how intrusive (social and financial) such ICDs had been based on clinical judgment.

Data analysis

All collected data were sent to the National Parkinson’s Centre of Excellence at Kings College Hospital in London, complying with the National Data Protection Act (UK registration no: Z6614305). Statistical analyses were performed using Stata 13.1 (StataCorp, College Station, Texas). For each recorded item descriptive statistics (central tendency and dispersion measures, proportions) were obtained. The chi-squared test was applied to compare categorical variables. A probability of an error less than 5% was regarded as significant.

Results

A total of 425 PD patients from 8 centres on DA treatment (initiated or already on) were included in this study (60.9% male; mean age= 68.3 years (range= 37-90); mean duration of disease= 7.5 years (range= 0-37)). Main PD-related historical data are shown in Table 1..

Regarding different DAs, 43.1% of the patients were on RTG TD patch (n=183) (mean final daily dose= 8.4 mg), 38.8 % (n=165) on ROP-XL (mean final daily dose =12.5 mg), and 17.9% (n=76) on PPX-PR (mean final daily dose= 2.9 mg). PPX-IR (mean daily dose = 2.6 mg) was taken by 105 and ROP-IR (mean daily dose =11.0 mg) by 43 patients, some of whom changed to PR DA’s during the course of the observation period. Treatment with dual agonists (oral DA with transdermal patch) at the same time was reported in 11.3 % of the evaluated cases. Only in one of these cases however, an ICD developed while on dual agonists and ceased when this agonist was discontinued.

Table 1: Main demographic and Parkinson’s disease historical characteristics

Demographic Characteristics	All cases (n=425)	ICD cases (n=57)
Male gender (%)	259 (60.9)	45 (78.9)
Mean Age in years (range)	68.3 (37- 90)	62.7 (42- 85)
Mean Age of Parkinson’s onset in years (range)	60.9 (18- 85)	55.7 (34- 85)
Mean Duration of disease in years (range)	7.5 (0- 37)	7.0 (0- 24)
Median Hoehn and Yahr stage (range)	2.5 (1.0- 5.0)	3.0 (1.0- 5.0)

No: Number; M: Male; F: Female

Of all assessed PD patients 13.4% (n=57/425) reported clinically relevant ICDs (Table 1; Mean age= 62.7 years, mean age of PD onset= 55.7, 79% male), ICD frequencies were 4.9% for patients on RTG patch, 13.9% for patients receiving ROP (14.0 % for ROP-IR, 13.9 % for ROP-XL) and 13.8% for patients on PPX therapy (19.0 % for PPX-IR, 6.6% for PPX-PR).(Table 2)

Table 2: ICD leading to discontinuation

	<b>Pooled PPX n=181</b>	<b>PPX-IR n=105</b>	<b>PPX- PR* n=76</b>	<b>Pooled ROP n=208</b>	<b>ROP-IR n=43</b>	<b>ROP- XL n=165</b>	<b>RTG n=183</b>
<b>ICD occurrence</b>	13.8 % (n=25)	19.0 % (n=20)	6.6 % (n=5)	13.9 % (n=25)	14.0 % (n=6)	13.9 % (n=23)	4.9 % (n=9)
<b>Mean dose All (ICD group)</b>	2.7 mg (2.8 mg)	2.6 mg (2.8 mg)	2.9 mg (2.7 mg)	12.2 mg (14.2 mg)	11.0 mg (19.2 mg)	12.5 mg (12.8 mg)	8.4 mg (11.3 mg)
<b>Mean LEDD All</b>	709.0 mg	771.8 mg	628.2 mg	597.4 mg	711.6 mg	572.6 mg	795.6 mg
<b>Mean LEDD ICD group</b>	935.6 mg	1020.8 mg	714.0 mg	605.1 mg	NA	522.4 mg	812.5 mg
<b>ICD leading to discontinuation</b>	7.2 % (n=13)	10.5 % (n=11)	2.6 % (n=2)	5.8 % (n=12)	9.3 % (n=4)	4.8 % (n=8)	2.2 % (n=4)
<b>Mean duration of therapy (All)</b>	33.0 months	45.9 months	15.4 months	23.3 months	30.4 months	20.4 months	21.3 months
<b>Mean duration of therapy (discontinued)</b>	26.7 months	29.7 months	9.9 months	18.3 months	22.3 months	14.9 months	14.3 months

ICD: impulse control disorder; PPX-IR: Pramipexole immediate release; PPX-PR: Pramipexole prolonged release; ROP-IR: Ropinirole immediate release; ROP-XL: Ropinirole extended release; RTG: Rotigotine; pooled: IR+ PR/XL; n: Number; ICD: Impulse control disorder; LEDD: Levodopa equivalent daily dose

\*PPX PR was marketed 36 months before end of study

Figure 1 shows the rates of ICDs on short and long acting DAs. The rate of ICDs with RTG was significantly lower ( $p < 0.05$ ) than ICD rates with any ROP formulation, or with PPX-IR or pooled PPX- (IR + PR). No significant difference between RTG and PPX-PR was observed. ICD rate with PPX-PR was significantly lower than with PPX-IR.



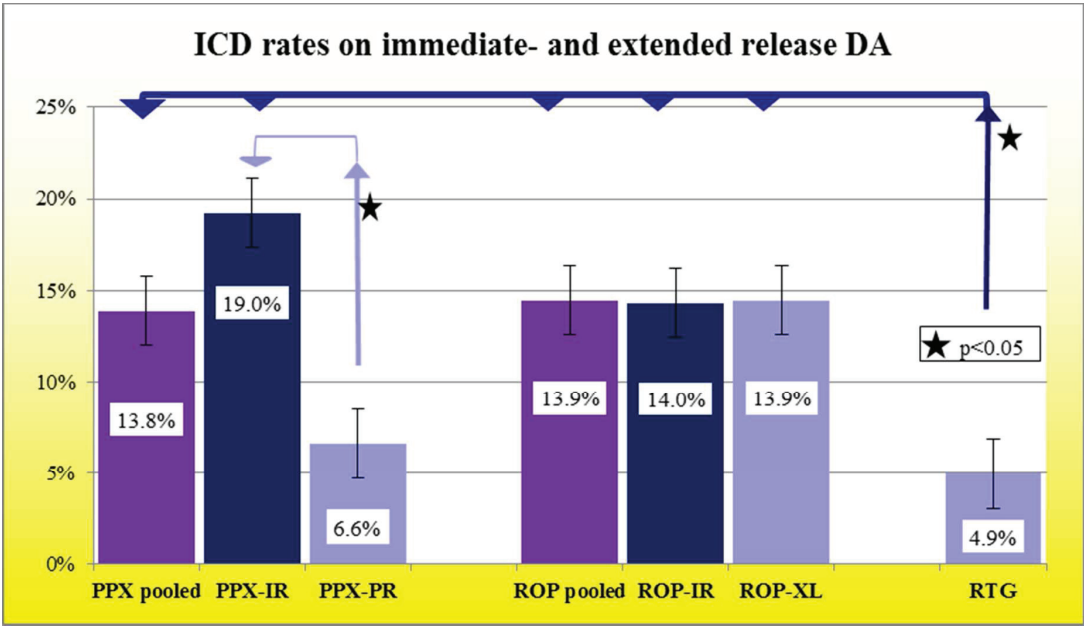


Figure 1: ICD rates on short and long acting Dopamine agonists

ICD: Impulse control disorder; DA: Dopamine agonists; PPX-IR: Pramipexole immediate release; PPX-PR: Pramipexole prolonged release; ROP-IR: Ropinirole immediate release; ROP-XL: Ropinirole extended release; RTG: Rotigotine; pooled: IR+ PR/XL; Chi-squared test,  $p < 0.05$

In terms of types of impulsive control behaviours, the reported ICDs included binge eating, gambling, compulsive shopping, hypersexuality, and hobbyism (Figure 2, table 3).

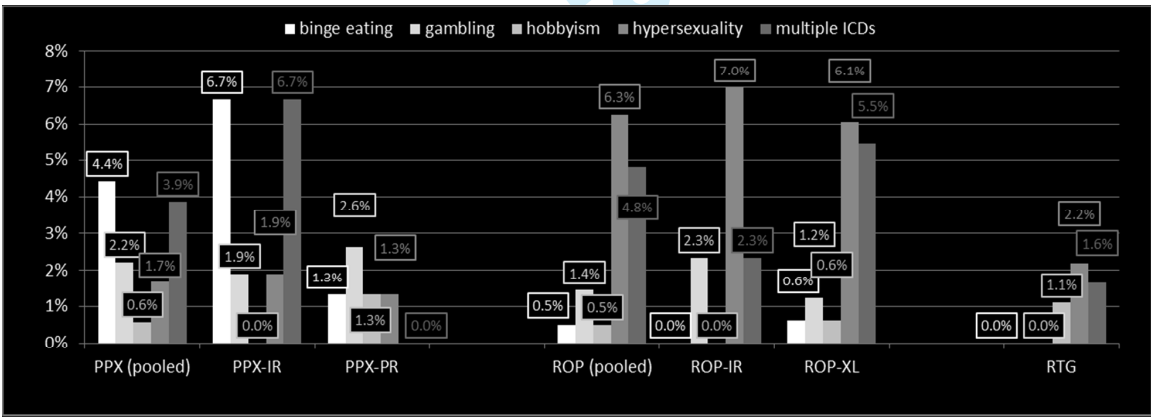


Figure 2: Type of impulse control disorder on different Dopamine agonists (% of patients on the respective drug)

PPX-IR: Pramipexole immediate release; PPX-PR: Pramipexole prolonged release; ROP-IR: Ropinirole immediate release; ROP-XL: Ropinirole extended release; RTG: Rotigotine; pooled: IR+ PR/XL



**Table 3: Type of impulse control disorder on different Dopamine agonists (% of patients on the respective drug, number of patients on the respective drug)**

	<b>Pooled PPX n=181</b>	<b>PPX-IR n=105</b>	<b>PPX PR n=76</b>	<b>Pooled ROP n=208</b>	<b>ROP- IR n=43</b>	<b>ROP- XL n=165</b>	<b>RTG n=183</b>
<b>ICD total occurrence</b>	13.8 % n=25	19.0 % n=20	6.6 % n=5	13.9 % n=25	14.0 % n=6	13.9 % n=23	4.9 % n=9
<b>Binge eating</b>	4.4 % n=8	6.7% n=7	1.3% n=1	0.5% n=1	0.0% n=0	0.6% n=1	0.0% n=0
<b>Gambling</b>	2.2% n=4	1.9% n=2	2.6% n=2	1.4% n=3	2.3% n=1	1.2% n=2	0.0% n=0
<b>Hobbyism</b>	0.6% n=1	0.0% n=0	1.3% n=1	0.5% n=1	0.0% n=0	0.6% n=1	1.1% n=2
<b>Hypersexuality</b>	1.7% n=3	1.9% n=2	1.3% n=1	6.3% n=13	7.0% n=3	6.1% n=10	2.2% n=4
<b>Multiple ICDs</b>	3.9% n=7	6.7% n=7	0.0% n=0	4.8% n=10	2.3% n=1	5.5% n=9	1.6% n=3

PPX-IR: Pramipexole immediate release; PPX-PR: Pramipexole prolonged release; ROP-IR: Ropinirole immediate release; ROP-XL: Ropinirole extended release; RTG: Rotigotine; pooled: IR+PR/XL; n= number; ICD: impulse control disorder

Occurrence of ICDs did not invariably lead to discontinuation of DA therapy; approximately half (50.9%) of all PD patients with ICDs discontinued DA therapy due to ICDs after a variable period following development of ICD. This reflected 2.2% (4 of 183) of PD patients treated with RTG, 4.8% (8 of 165) with ROP-XL, and 2.6% (2 of 76) with PPX-PR. Mean dose and mean duration of therapy were similar for ICD patients who discontinued versus those who did not discontinue DA treatment.

Of the ICD cases 59.6% reported having been treated with IR DAs previously.

**Discussion**

In this real life observational multicentre survey, we report on some observations about DA treatment in real life practice:

- A. ICD rates with RTG (4.9%) patch as well as with PPX-PR (6.6%) were significantly lower compared with other DA formulations.
- B. 50.9% of PD patients presenting with ICDs had to discontinue DA therapy. Further subanalysis suggests that frequencies of discontinuation due to ICDs for PR DAs or RTG therapy among the sample were low, ranging from 2.2% for TD RTG and 2.6% for PPX-PR, to 4.8% for ROP-XL
- C. Various types of ICDs were reported, hypersexuality appearing to be the most prevalent ICD in the ROP group, for both IR and XL preparations.

These observations however, need to be considered in the context of a real life observational study and as such methodological limitations in relation to comparison of ICD rates apply.

Patients were included who started on relevant therapies (long acting DA and TD RTG) during a specific period in multiple centres using similar clinical protocols. We therefore have no control over the subject demographics and in this sense this is a real life study not restricted by strict inclusion and exclusion criteria employed in controlled clinical trials. Patients with clinically relevant dementia as per clinical judgement were not included, as these would not be considered for DA treatment according to clinical practice. Also other confounders such as Levodopa induced dyskinesias were not assessed.

Additionally, we were unable to exclude the effect of previous therapies on observed ICDs. We also did not use specific validated tools such as the QUIP for screening or diagnosing ICD cases but instead relied on detailed clinical interview by experienced clinicians to address clinically relevant ICD rates. Nevertheless, we believe this observational report has collected important data regarding ICDs related to PR DAs for the first time from a multicentre study.

Analysis of this European multicentre case note and prospective interview based survey including 425 PD patients from all stages of the disease and all age groups show a relatively low frequency of ICDs with the use of PR DAs. The overall occurrence of ICDs was 13.4% in patients taking short- or long acting DAs in our cohort and this issue merits discussion.

There is a wide range in the reported prevalence of ICD in PD among several different studies. Some studies are broadly in agreement with our study [5, 9] whereas other studies have shown higher rates of ICDs [10, 8, 11, 12]. This variation is likely to be due to several factors including: the method of assessment (such as use of the QUIP, detailed interview, use of other scales); whether only bothersome ICDs (pathological as defined by Ondo and Lai [13]) were included; and the number of cases included in the study.

These varying datasets underpin difficulties in ascertainment of ICDs in real life population studies as well as the problem of using varying methodologies. The key issue however, is that to our knowledge, ours is the only study which has addressed the issue of ICDs and the use of long acting DAs (PPX-PR and ROP-XL) and continuous drug delivery (RTG) and attempted a comparison in a real life population in a multicentre set up, which has been an academically led as opposed to an industry funded study.

In detail, our results are in agreement with the results published by Garcia-Ruiz et al (2014) who reported that RTG patch appears to have a significantly lower rate of ICD compared to other short- or long acting DAs [7]. The reason for the lower rates of ICDs with PPX-PR and RTG versus a high rate with ROP-IR and XL even at a modest dose is unclear. We hypothesised that the pattern of drug delivery may influence unmasking of ICDs and in this context use of drugs utilising the continuous drug delivery concept may be beneficial [14]. The low rates of ICDs with PPX-PR and RTG patch compared to high rates on PPX-IR and ROP- IR support the above hypothesis but the data related ROP-XL may not. We are unable at this time to explain this discrepancy. In table 3 we report the mean doses of the DA and the rate of actual discontinuation of therapy in patients with ICDs. This is a crucially relevant clinical issue. The doses are variable and in case of ROP range from 11.0 mg in the IR arm to 12.5 mg in the XL arm. This suggests that ICDs, even when intrusive and requiring discontinuation of relevant therapy can occur at relatively low doses of the DA. In the ROP-XL arm, therapy had to be discontinued due to ICDs after more than a year (average of 14.9 months) of therapy suggesting a delayed onset of ICDs in some cases. The overall rates of discontinuation of therapy due to DAs were low and this could be linked to the awareness of investigators to the possibility of development of dopamine agonist withdrawal syndrome (DAWS) [15]. This could have prompted continuation of DAs but at lowered doses, however we were unable to capture this data in this study. Our data is also supported by a recent study by Antonini et al. (2015) who screened ICD cases reported among 786 subjects involved in various clinical trials utilising RTG patch, from data held on file by UCB pharmaceuticals [16]. Overall a low ICD rate of 9% was reported with only 2.8% graded as severe ICD requiring discontinuation of RTG. This observation also reinforces the clinical concept that in many patients, DAs can indeed be continued in spite of ICDs but with close monitoring and education of patient and carer thus avoiding the damaging clinical and psychological effect of DAWS [17]. This concept underpins the recent recommendation for management of ICDs [14].

The patterns of ICDs noted in this study are shown in figure 3 and conforms to the established variants of ICDs described in literature. The patterns were noted as based on clinical interview and reporting. Hypersexuality was common in those on ROP while binge eating and hobbyisms (which included compulsive shopping) were also represented but compulsive gambling was relatively low in numbers. The explanation for this is unclear although, perception of gambling being an ICD and an adverse effect of DA therapy is high among patient groups and medical staff and could have led to being alert to this issue with a resultant early intervention and consequent low rate of troublesome gambling. Multiple types of ICDs were also noted among all DAs.

It is inevitable, that an observational survey based study such as this will carry several limitations. These have been outlined at the beginning of the discussion and we are not forwarding any recommendation regarding choice of DA therapy and risk of ICDs based on this study. This is because, firstly this was not a controlled study but an open label observation of real life clinical practice generated datasets using a common data sharing network in a convenience sample. As such the three groups of patients on PR DAs and RTG TD patch could not be matched in terms of prior exposure to DA or overall Levodopa equivalent daily dose. We also did not use the QUIP questionnaire [18, 19] but relied on the NMS Questionnaire and clinical interviews for detection of ICDs and determinations of its intrusive effect on their lives. One may argue therefore, that we underestimated the rates of overall ICDs, recreational, problematic as well as pathological [13] however we specifically sought to address discontinuation rates due to ICDs as well. The latter, we believe would have successfully addressed pathological and problematic ICDs. We accept however, that lack of use of tools such as the QUIP may have allowed an underestimate of the rates of ICD overall including those where the problem may not be clinically intrusive. However, in clinic, it is often the pathological ICDs that are of greatest concern.

The combination of short acting and long acting DA use in some of our patients makes this comparative analysis difficult to perform and as such the data interpretation needs to be tailored addressing this confounding effect. Furthermore, the length of exposure of DAs varies between the different formulations which could also account for some of the differences. However, in spite of the mentioned drawbacks, there are strengths of this study such as the prospective multicenter survey based data as well as a reasonable number of patients in each DA group obtained from 8 independent contributing international centres. Furthermore, the mean duration of therapy with DAs is higher than 15.4 months allowing us to speculate on long term effects. In part, based on these observations, a recent review for treatment recommendations in ICD, advocate the consideration of switching of patients developing ICD on short acting DA therapy to transdermal or other non-oral strategies utilising constant drug delivery pattern [13]. Needless to say that such patient need close monitoring after the switch regarding the state of their ICD.

In conclusion, the results of this international observational multicentre survey of clinically relevant ICD rates with currently used DAs appear to be variable depending on the formulation (IR or PR) except for ROP-XL, rates being lower with RTG patch and PPX-PR. However, we are not able to make any recommendations based on this as this was not a randomised controlled study and also the patients groups were not matched in terms of Levodopa equivalent daily doses. Nevertheless, the data, obtained from multiple sources should form the basis of further controlled comparative studies addressing the issue of clinical use of long acting and TD dopamine agonists and ICDs.

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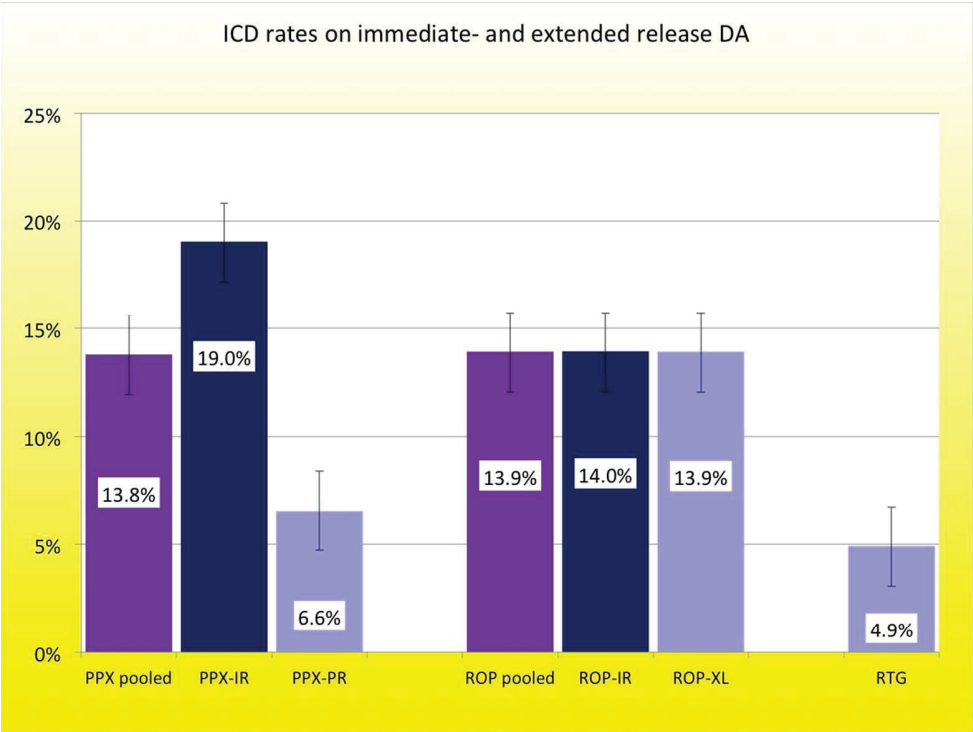


Figure 1: ICD rates on short and long acting DA's

ICD: Impulse control disorder; DA: Dopamine agonists; PPX-IR: Pramipexole immediate release; PPX-PR: Pramipexole prolonged release; ROP-IR: Ropinirole immediate release; ROP-XL: Ropinirole extended release; RTG: Rotigotine; pooled: IR+ PR/XL; Chi-squared test,  $p < 0.05$

451x338mm (72 x 72 DPI)

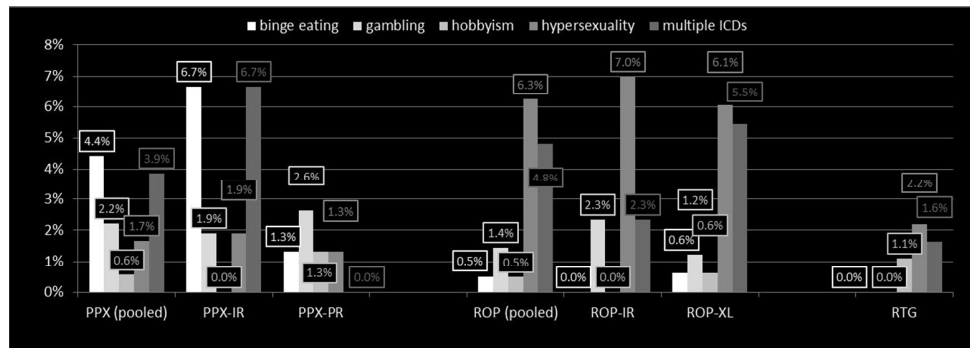


Figure 2: Type of impulse control disorder on different Dopamine agonists (% of patients on the respective drug)

PPX-IR: Pramipexole immediate release; PPX-PR: Pramipexole prolonged release; ROP-IR: Ropinirole immediate release; ROP-XL: Ropinirole extended release; RTG: Rotigotine; pooled: IR+ PR/XL

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**Table 1: Main demographic and Parkinson’s disease historical characteristics**

Demographic Characteristics	All cases (n=425)	ICD cases (n=57)
Male gender (%)	259 (60.9)	45 (78.9)
Mean Age in years (range)	68.3 (37- 90)	62.7 (42- 85)
Mean Age of Parkinson’s onset in years (range)	60.9 (18- 85)	55.7 (34- 85)
Mean Duration of disease in years (range)	7.5 (0- 37)	7.0 (0- 24)
Median Hoehn and Yahr stage (range)	2.5 (1.0- 5.0)	3.0 (1.0- 5.0)

No: Number; M: Male; F: Female

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Table 2: ICD leading to discontinuation

	<b>Pooled PPX n=181</b>	<b>PPX-IR n=105</b>	<b>PPX- PR* n=76</b>	<b>Pooled ROP n=208</b>	<b>ROP-IR n=43</b>	<b>ROP- XL n=165</b>	<b>RTG n=183</b>
<b>ICD occurrence</b>	13.8 % (n=25)	19.0 % (n=20)	6.6 % (n=5)	13.9 % (n=25)	14.0 % (n=6)	13.9 % (n=23)	4.9 % (n=9)
<b>Mean dose All (ICD group)</b>	2.7 mg (2.8 mg)	2.6 mg (2.8 mg)	2.9 mg (2.7 mg)	12.2 mg (14.2 mg)	11.0 mg (19.2 mg)	12.5 mg (12.8 mg)	8.4 mg (11.3 mg)
<b>Mean LEDD All</b>	709.0 mg	771.8 mg	628.2 mg	597.4 mg	711.6 mg	572.6 mg	795.6 mg
<b>Mean LEDD ICD group</b>	935.6 mg	1020.8 mg	714.0 mg	605.1 mg	NA	522.4 mg	812.5 mg
<b>ICD leading to discontinuation</b>	7.2 % (n=13)	10.5 % (n=11)	2.6 % (n=2)	5.8 % (n=12)	9.3 % (n=4)	4.8 % (n=8)	2.2 % (n=4)
<b>Mean duration of therapy (All)</b>	33.0 months	45.9 months	15.4 months	23.3 months	30.4 months	20.4 months	21.3 months
<b>Mean duration of therapy (discontinued)</b>	26.7 months	29.7 months	9.9 months	18.3 months	22.3 months	14.9 months	14.3 months

ICD: impulse control disorder; PPX-IR: Pramipexole immediate release; PPX-PR: Pramipexole prolonged release; ROP-IR: Ropinirole immediate release; ROP-XL: Ropinirole extended release; RTG: Rotigotine; pooled: IR+ PR/XL; n: Number; ICD: Impulse control disorder; LEDD: Levodopa equivalent daily dose

\*PPX PR was marketed 36 months before end of study